Richard L. Wolgemuth, Ph.D.
Senior Vice President
Global Regulatory Sciences
Pharmaceutical Research Institute

P O Box 4000 Princeton NJ 08543-4000
Tel 609-252-6503 Fax 609-252-7350
Richard.Wolgemuth@bms.com

Bristol-Myers Squibb Company

July 9, 2004

Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2004D-0188; BMS ID No. 0496. Draft Guidance, Development and Use of Risk Minimization Action Plans *(Federal Register May 5, 2004)*

Dear Sir or Madam:

Bristol-Myers Squibb (BMS), a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, infant formulas, and nutritional products, is pleased to have the opportunity to offer comments on the Draft Guidance on Development and Use of Risk Minimization Action Plans. Our company's mission is to extend and enhance human life by providing the highest-quality pharmaceutical and related health care products. Our comments are set forth below.

Summary of BMS Comments on Proposal

BMS commends the FDA for undertaking the development of the Draft Guidance document that describe the FDA's philosophy and approach to Development and Use of Risk Minimization Action Plans (RiskMAPs). Overall, BMS is in agreement with the framework of this Guidance. BMS agrees with the FDA that risk assessment/risk minimization efforts must include both benefit and risk evaluations throughout the lifecycle of a given product. BMS concurs that most products will not pose an unusual type or level of risk requiring additional risk minimization efforts beyond professional labeling. However, the document would benefit from increased clarity regarding methodology for the assessment of benefit/risk balance and the Agency's plans for setting uniform standards across products and review divisions relative to interpretation of benefit/risk information and the implementation of RiskMAPs.

BMS welcomes partnering as early as feasible with the FDA review division and other FDA working groups, e.g., representatives from the Office of Drug Safety (ODS), during product development to maximally foster timely and open discussions of safety concerns and the potential need for development of a RiskMAP. The Guidance document would benefit, however, from setting forth a more systematic and formal approach to the timing and staging of these discussions so that uniform

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communication procedures are carried out across products and review divisions throughout the product development lifecycle. Concurrence of FDA divisions is equally important and should be formally enabled through the reviewing division structure.

Specific Comments (Items that Need Clarification & Recommended Actions)

Iterative risk assessment and risk minimization (Section II.B., lines 51-63):
BMS agrees with the FDA that assessments must include both benefit and risk considerations and concurs with the FDA regarding the iterative 4-part process of risk assessment and risk minimization throughout a product's lifecycle. BMS anticipates that both benefits and risks warrant updates to address a changing benefit-risk balance, particularly since benefit may not be fully optimized until later in the lifecycle of the product.

Risk definitions:

- Known risk (Section I., lines 19-22). The draft Guidance provides industry with recommendations on initiating and designing RiskMAPs to minimize "known risks." BMS suggests including a definition of "known risk" that would consider it to be the specific product risk at a particular point in time, taking into consideration all information, including, but not limited to, class pharmacologic effect, animal and human study data, and data from the literature.
- Individual patient risk (Section I. A., lines 134-137). Both benefits and risks are defined in this Draft Guidance as being patient-specific. However, some benefits and risks may apply to a specific population rather than to individual patients (e.g., public health benefit or risk). The final Guidance should clarify if RiskMAPs are to be designed only to minimize individual patient risks or whether they are to be applied for potential risks to a population (e.g. development of resistance to antimicrobial agents).

Comparison of benefit and risk (Section III.A., lines 117-138; Section III.D., lines 212-217):
BMS concurs with the FDA that comparison of benefits to risks may be complicated and multi-faceted and that a major difficulty in such assessments is that different units are used to measure benefit and risk. Thus, it may not be possible to quantitatively weigh the nature and rate of known risks against the magnitude and duration of benefits. However, in that the benefit/risk balance provides the foundation for all risk management activities, BMS would welcome guidance from the FDA as to more specific methodology that can be uniformly applied for consistent benefit/ risk assessments, particularly when comparison of benefit/risk balance across a group of products is desirable.

To strike a proper balance between benefit and risk, BMS suggests an approach utilizing epidemiological projections of benefit, recognizing that such projections may involve the use of risk reduction from surrogate level markers. In this manner, the benefit/risk balance may potentially be addressed quantitatively in terms of projected adverse outcomes avoided.

FDA's interpretation of whether a Risk MAP is needed (Section III., lines 113-115; Section III.D., lines 203-4; 212-213:
BMS concurs with the FDA that most products will not pose an unusual type or level of risk

requiring risk minimization efforts beyond product labeling, and BMS seeks opportunities to partner with the FDA in formulating an interpretation of whether a RiskMAP is needed. BMS concurs that all relevant information should be evaluated that helps identify if a RiskMAP could improve the benefit-risk balance of a given product. If the risk concern is of non-human origin, additional reliance upon extrapolation of benefit may be warranted. In the event the FDA recommends that a sponsor consider a RiskMAP based on the Agency's own interpretation of risk information, BMS suggests that the FDA formally alert the sponsor as soon as this determination has been made and promptly initiate discussions among the review division, ODS, and the sponsor. Given the impact that the development of Risk MAP tools and evaluation activities may have on timelines relative to product launch, it would be beneficial if periodic and systematic reviews of benefit and risk of products being investigated under INDs were undertaken by FDA and any differences in interpretation of risk information relative to those of the sponsor promptly communicated.

Tools:

- Targeted education and outreach (Section IV.B., lines 284-285). BMS recommends that the Guidance include a much clearer statement regarding the use of "focused or limited" promotional techniques such as product sampling or direct-to-consumer advertising. The FDA should clarify whether product sampling is permitted only under certain conditions (e.g. discouraged unless immediate initial supply to patients is a critical factor in treatment) and whether direct-to-consumer advertising is prohibited or subject to certain restrictions for drugs which are covered by a RiskMAP.
- Use of reminder systems (Section IV.B.2, lines 298-320, Section IV.D., lines 372-387). BMS concurs with the FDA as to the importance of using tools with the least burdensome effect on health care practitioner-patient, pharmacist-patient, and/or other health care relationships in order to maintain the widest possible access compatible with adequate risk minimization. Patient agreement or acknowledgement forms, certification programs for practitioners, and physician attestation of capabilities should be judiciously employed as tools to assist healthcare providers in their interactions with patients and not as inadvertent barriers to patients for whom a positive product benefit/risk balance might be realized. BMS notes that health care providers may interpret these tools as a means of shifting the responsibility and liability for product safety solely onto them; thus, they may decide not to prescribe products with RiskMAPs and alternatively, may prescribe products with less optimal benefit/risk balances for the disease under treatment.

Assessment of RiskMAP effectiveness:

- Use of descriptive statistics (Section V.A., lines 468-471) vs. Section VII.A., lines 770-773 and B., lines 813-819)). In Section V, the Guidance suggests that descriptive statistics are sufficient and that statistical hypothesis testing would not typically be expected given the limitations of the data likely to be available. This advice conflicts with the information in Section VII, where the Guidance implies it is appropriate to set statistical criteria to assess whether the targeted values for each measure have been achieved and to describe power and precision of estimates.
- Validity of measures (Section V., lines 502-4). BMS concurs with the FDA that the validity of a measure may be judged by how closely it is related to the desired health outcome goal of the RiskMAP. However, it will be useful in the Guidance to clearly articulate when a

measurement instrument, as opposed to a measure of effectiveness, requires formal validation.

- Use of population-based evaluation methods to assess RiskMAP effectiveness (Section V. B. 2., lines 522-530). BMS concurs with the FDA that population-based evaluation methods can be used to estimate the rate of events. However, depending upon the specific data source used, there can be a significant lag time between the dates of occurrences of events and timing relative to the ability to retrieve and analyze such data.

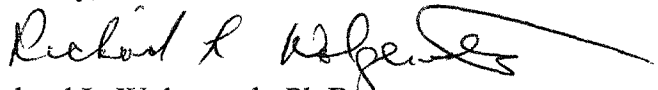
Communicating with the FDA (Section VI., lines 644-664; also relates to Section III.D., lines 203-204):

BMS recommends that discussions between the FDA and the sponsor regarding a potential Risk MAP occur as early as possible in the development of a given product. BMS concurs with the FDA that natural intervals to discuss RiskMAP issues can be pre-defined, such as at end-of-phase-2 meetings.

The FDA and the sponsor should be encouraged to alert the other party in a timely manner to facilitate the discussion of a potential benefit/risk issue. BMS welcomes partnering as early as feasible with the FDA review division and other FDA working groups, e.g., representatives from the Office of Drug Safety (ODS), during product development to maximally foster timely and open discussions of safety concerns and the potential need for development of a RiskMAP. The Guidance document would benefit, however, from setting forth a more systematic and formal approach to the timing and staging of these discussions so that uniform communication procedures are carried out across products and review divisions throughout the product development lifecycle. Concurrence of FDA divisions is equally important and should be formally enabled through the reviewing division structure.

BMS appreciates the opportunity to provide comment and respectfully requests that the FDA give consideration to our recommendations. BMS would be pleased to provide additional pertinent information as may be requested.

Sincerely,



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